PATENT
Attorney Docket No. Shi/Anderson I (2101363/991000)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Shi and Anderson

Serial No.: 09/378,577

Filed: August 20, 1999

For: METHOD FOR THE TREATMENT AND PREVENTION OF DENTAL CARIES

Group Art Unit: 1645

Examiner: Robert Zeman

CERTIFICATION UNDER 37 CFR 1.8

I hereby certify that the documents referred to as enclosed herein are being deposited with the United States Postal Service as first class mail with sufficient postage on this date, January 27, 2003, in an envelope addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231

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APPELLANTS' BRIEF ON APPEAL SUBMITTED PURSUANT TO 37 CFR §1.192

In support of the notice of appeal filed on November 25, 2002, Appellants submit their Brief on Appeal, in triplicate.

Enclosed is a check for $320.00 as required under 37 CFR §1.17 (c) for the filing of this Brief. Please charge any additional fees, or make any credits, to Deposit Account No. 07-1896.

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I. REAL PARTY IN INTEREST

The real parties in interest in this appeal are C3 Scientific Corporation, Seattle, Washington and The Regents of the University of California, Oakland, CA, the owners of this application.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS ON APPEAL

A copy of the claims as they presently stand on appeal is included as Appendix A. The pending claims are claims 1-4, 6-10, 12 and 17.

IV. STATUS OF AMENDMENTS

A Response to Final Office Action under 37 C.F.R. § 1.116 was submitted on November 24, 2002. In the response, claims 3, 7, and 9 were amended. The Advisory Action mailed on November 1, 2002 indicates that the amendments will be entered upon Appeal.

V. SUMMARY OF INVENTION

The present invention takes on a unique approach to treat and prevent dental caries. Prior to the present invention, the conventional wisdom for treating dental caries was to remove cariogenic bacteria and prevent them from colonizing on dental surfaces, *e.g.*, using antibodies to cause bacterial aggregation thus prevent them from adhering to dental surfaces.

The present invention provides a new and effective way of combating cariogenic bacteria by using specifically designed antibodies to harness subject's own humoral immune response. Such an approach and way of thinking was drastically different from what was known

in the prior art disclosure. The methods provided by the present invention utilize specifically designed antibodies to engage the subject's own immune system in order to kill the cariogenic bacteria instead of just blocking their colonization on dental surfaces. Specifically, the methods provided by the present invention use a particular group of antibodies with the ability to trigger the subject's own humoral immune responses to selectively kill cariogenic organisms.

The claims of the present invention are directed to methods of treating or preventing dental caries by administering chimeric antibodies that having recited abilities, i.e., 1) specifically bind to a cariogenic organism and 2) elicit a humoral immune response in the subject against the cariogenic organism.

VI. EXAMINER'S REJECTIONS

The Examiner has rejected the claims as obvious by selectively picking through disclosures from the two cited references (Ma and Adair) and combining these isolated disclosures in hindsight to try to reach the present invention. For example, among the three different forms of antibodies disclosed in Ma, the examiner selectively picked a single form of antibody related to the methods provided by the present invention and left the two other forms of antibodies that are irrelevant to the methods provided by the present invention without providing any evidence or reasoning why such specific selection is obvious to one skilled in the art. The examiner's selection is especially troublesome in light of the fact that Ma believed that the two modified antibodies not selected by the examiner could be more effective in treating dental caries.

Furthermore, the examiner out of thin air combined the selected single form of antibody in Ma with an antibody modification method in Adair, despite the fact that such method is specific to an antibody not relevant to dental treatment and an antibody modified according to the method provided by Adair may or may not function properly because of the modification.

Pressed by the applicants' request for the basis of the rejection, the examiner resorted to "inherency teaching" and in essence assumed that a skilled artisan would have had the "right instinct" to wade through myriads of choices and end up in the right direction towards the present invention. The examiner has yet to provide any evidence or reasoning to support such

assumption, especially in response to the reference's own teaching away from the choices the examiner would like to project on one skilled in the art at the time of the invention.

For example, Ma provided three different antibodies and the examiner simply assumed that one skilled in the art would have had the "right instinct" to choose the single right form of antibody out of all three antibodies for the modification method provided by Adair. In other words, the examiner simply assumed that one skilled in the art would have stayed away from the other two antibodies that were promoted by Ma and irrelevant to the present invention. The examiner further assumed that one skilled artisan would have had reasonable expectation of success using the modified antibody despite the fact that the activity required of the modified antibody is out of ordinary and not naturally existing in the systems to be treated. The examiner in essence requires one skilled artisan on his or her own initiative to be able to create an antibody specifically useful for the approach used by the present invention without any appreciation of the approach used by the present invention, *e.g.*, a classic reflection of impermissible hindsight.

VII. ISSUES

1) Whether the examiner has set forth a prima facie case of obviousness in rejecting claims 1-4, 6-10, 12, and 17 based on cited prior art.

2) Whether the examiner can rely on inherency to reject claims 1-4, 6-10, 12, and 17 as obvious over cited prior art.

VIII. GROUPING OF CLAIMS

The claims are grouped as the following.

Group I. Claims 1-4 and 6 stand or fall together.

Group II. Claims 7-10, 12, and 17 stand or fall together.

IX. ARGUMENT

1. A prima facie case of obviousness has not been set forth because Ma in view of Adair does not teach or suggest the present invention.

The present invention is directed to methods of treating and preventing dental caries by administration of a chimeric antibody that 1) specifically binds to a cariogenic organism,

and 2) elicits a humoral immune response. The Ma reference in combination with Adair cited by the Office Action do not teach or suggest using the particular type of antibodies used by the present invention. On the contrary, Ma teaches away from the present invention, *e.g.*, teaches away from using chimeric antibodies that elicit the humoral immune response as required by the present invention.

Specifically Ma is directed primarily to expressing a murine IgG1 antibody, Guy's 13, in transgenic plants. According to Ma, Guy's 13 prevents adherence and colonization of *S. mutans in vivo* by binding to the surface of the bacteria and does not function as an antibody that engages the subject's immune system to elicit humoral immune responses.

As it is commonly known in the field, an antibody can be generally divided into two portions: the F(ab)2 portion (the variable region) and the Fc portion (the constant region). See Figure 1 in Appendix B. The F(ab)2 portion is involved in the specific binding of an antibody to an antigen while the Fc portion is involved in engaging the effector apparatus of the system, *e.g.*, eliciting humoral immune response.

Ma specifically teaches that humoral immune response is not related to the function of the antibody since "[t]he Fc-mediated functions of the mAb were not essential, as the F(ab')2 portion was as protective as the intact IgG,...." (See page 131, bottom of the left column, emphasis added). Ma further concludes at the end of the article that the functional regions of the antibody involved in humoral immune response are not essential, stating " [a]lthough the maintenance of bivalent antigen binding of the antibody molecule was required for prevention of colonization of *S. mutans in vivo,* the functional Ig regions that are involved in complement binding and opsonization through cellular interactions [e.g., humoral immune response] are not essential." (See page 136, last paragraph).

Therefore, Ma clearly teaches that the epitope binding of the Guy'13 antibody is critical to its protective function against *S. mutans* whereas Fc-mediated functions of the antibody such as eliciting a humoral immune response through complement binding or cellular interactions is dispensable since deletion of the Fc region of the Guy's 13 did not have any impact on the protective effect of Guy's 13.

Based on such teaching, one skilled artisan would have been motivated to focus on the binding activity of the antibody and the regions associated therewith, but not the

functional regions that are involved in engaging the subject's own immune response. In other words, one skilled artisan would have been motivated to delete the functional regions that are associated with eliciting humoral immune response in the subject or replace it with other regions that are useful for the binding activity of the antibody, especially blocking the bacterial colonization.

Ma further motivates such action by demonstrating that deletion of the functional regions associated with eliciting humoral immune response does not affect the intended binding and blocking function of the antibody disclosed in the prior art. Ma tested the expression of not only Guy'13, but also two other IgG-IgA hybrids of Guy's 13 to see whether the constant region of IgA, which is known to be irrelevant to triggering humoral immune responses, can enhance the protective effect of Guy's 13. The constant region of IgA does not include a complete Fc region[1], thus does not trigger Fc-mediated humoral immune response in mucosal environment. Ma believes, however, that the constant region of IgA increases the valency and resistance to proteolytic activity of the IgG-IgA hybrid antibody and is advantageous, especially when the bacterial aggregation is the important effector mechanism. (See the last paragraph of page 136 and the first paragraph of page 137.) Therefore, by replacing a large part of the IgG constant region with the IgA constant region, Ma has truncated the Fc region of IgG and followed its own teaching that the constant regions responsible for eliciting humoral immune response are not important for the treatment of dental caries and can be deleted without affecting the function of the antibody.

Based on the data obtained from the hybrid antibodies, Ma concludes that for the protective effect offered by Ma's antibody, the regions responsible for eliciting humoral immune response not only can be deleted, but also can be replaced by other constant regions that do not contain a functional Fc region for eliciting humoral immune response. Therefore, Ma does not teach or suggest using antibodies capable of eliciting humoral immune response to treat or prevent dental caries. To the contrary, Ma teaches that the "goal" is to use antibodies capable of causing bacterial aggregation, and regions of antibodies associated with

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[1] The Fc region includes CH2 and CH3. The constant region of IgG includes CH1, CH2, and CH3 whereas the constant region of IgA includes CH1 and CH2.

eliciting humoral immune response can and should be deleted and replaced with regions that enhance the binding and blocking activity of the antibody useful for Ma's method of treating or preventing dental caries.

The Office Action states that in view of Adair, one skilled in the art would have "humanized" the antibody used in Ma, implying any humanized version of the antibody in Ma would be useful for the present invention. Applicants respectfully point out that Adair discloses the humanization of a specific antibody against carcinoembryonic antigen. Antibodies against carcinoembryonic antigens bear no functional similarity with the antibodies against cariogenic organisms used in Ma. It is hindsight to assert that just because one specific antibody is humanized, then the humanization of another totally different antibody which functions in an entirely different environment is obvious.

As it is well known, an antibody's activity is closely related to the antibody's three-dimensional structure. Humanizing an antibody means replacing part of the non-human antibody with a portion of the antibody from humans. After such humanization, it is always uncertain whether the human portion of the antibody is compatible with the non-human portion. Specifically after each "humanization", there is always a question mark whether the humanized version can still fold correctly to maintain the original three-dimensional structure and whether the humanized version can still maintain the original activity. The publication of Adair's or others' result that one particular antibody can be humanized illustrates exactly how uncertain it is to humanize each individual antibody.

Therefore, even if one skilled in the art decided on his or her own initiative to humanize the antibody used in Ma based on the methods provided in Adair, it would have been at most "obvious to try" without any reasonable expectation of success since for each specific monoclonal antibody, one would have had to determine how much human antibody portion should be included and whether the humanized version will retain the binding specificity and activity of the original antibody.

For the present invention, in addition to the general uncertainty of humanizing particular antibodies there is another level of unpredictability associated with whether humanized antibodies can elicit humoral immune responses in the subject to be treated. The examiner has yet to provide any evidence or reasoning as to why one skilled artisan would

have humanized the antibody in a way that would trigger humoral immune response. Furthermore, the examiner has yet to establish why one skilled artisan would have had reason to believe that any humanized antibody would elicit humoral immune response when such response does not naturally exist in the environment associated with cariogenic organisms.

Specifically to humanize an antibody, one usually has to decide which constant region of the human antibody and how much of it should be used to replace the original antibody. In the present case even if one had decided to try the humanization of the antibody provided in Ma, one would have had to choose a constant region from various types of human antibodies, *e.g.*, IgG, IgA, etc. According to Ma, one would have chosen IgA constant region which was believed useful for binding and blocking function of the antibody, but not for triggering humoral immune response, and such humanized antibody would not be useful for the methods provided by the present invention. Specifically Ma has taught in its disclosure that IgA is the preferred antibody type to use for the treatment of dental caries. Ma believes that the antibody functions via blocking the bacterial aggregation on dental surface and that IgA version of the antibody has increased valency and resistance to proteolytic activity which can be advantageous in causing bacterial aggregation for the treatment of dental caries. (See the first paragraph of page 137.). Therefore, even if one skilled artisan were motivated to humanize the antibody provided in Ma, he or she would have followed Ma's teaching and made humanized antibody useful for causing bacterial aggregation but not for the present invention in triggering humoral immune response for the treatment of dental caries.

Furthermore, for the purpose of argument even if we assume that one skilled in the art would have humanized the antibody provided by Ma and would have humanized it in a way that is capable of triggering humoral immune response despite the opposite teaching in Ma, one skilled artisan still would not have had any reasonable expectation that such antibody would be able to elicit a humoral immune response since it was greatly uncertain whether the environment harboring cariogenic organisms can support a humoral immune response. It has been well known that the environment harboring cariogenic organisms usually lacks endogenous antibodies that are associated with humoral immune responses. Most antibodies that naturally exist in the environment of cariogenic organisms, *e.g.*, mouth do not engage subject's own immune system to elicit humoral immune response. In other words, the

present invention provides a method of using a particular antibody to induce the humoral immune responses that normally do not occur in the subject. Therefore it would have been uncertain at the time prior to the present invention whether chimeric antibodies introduced exogenously would be able to successfully engage the subject's immune system and elicit a humoral immune response that was not naturally occurring.

In summary, the examiner simply has not made a prima facie case of obviousness. The rejection is based primarily on hindsight and requires one skilled artisan to ignore Ma's promotion of the type of antibodies useful for causing bacterial aggregation, but not for eliciting the humoral immune responses required by the present invention. The rejection in essence is hinged on a series of assumptions that one skilled artisan, in the absence of any specific teaching and suggestion, would have 1) humanized the antibodies used in Ma, 2) humanized the antibodies to a type that was not promoted by Ma, but was chosen by Ma to modify away from, 3) reasonably expected that such humanized antibody would retain the specification and binding activity of the original antibody, and 4) reasonably expected that such humanized antibody would function in a method not taught or suggested by Ma. The examiner made these assumptions largely on impermissible hindsight and has yet to provide any evidence to support these assumptions. Therefore, the examiner has failed to make a prima facie case of obviousness.

2. Inherency of an advantage and its obviousness are different questions; that which may be inherent is not necessarily known; obvious cannot be predicted on which is unknown. ***In re Spormann*** **363 F.2d 444, 150 U.S.P.Q. 449, (CCPA 1966)**

The examiner seems to imply that the obviousness rejection may be based on alleged inherent teaching of the cited prior art. Applicants respectfully point out that an obviousness rejection has to rely on what is taught by the prior art, not what is inherent or allegedly inherent in the prior art and not necessarily known to one skilled artisan.

The Office Action asserts that "inherent teaching" of a prior art reference arises both in the context of anticipation and obviousness. *In re Napier* 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). Applicants respectfully point out that "inherent teaching" if used in the obviousness rejection has to be necessarily known to one skilled in the art. Such

standard is specifically followed in *In re Napier*, where the Board relied on the teaching of a second prior art reference to support the position that the inherent disclosure by the first prior art was known to one skilled in the art prior to the invention at issue, *e.g.*, based on the second prior art the disclosed means for noise reduction in the first prior art also necessarily known to others, as suggesting another means for noise reduction, thus makes the other means for noise reduction obvious. (*Id.* at 1784.)

The Office Action also cites *In re Grasselli* 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and *In re King* 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986) to support its position. Applicants respectfully point out that in *In re King*, the Court opinion is solely directed to anticipation issues and is not directed to inherency in obviousness rejection. Since the standards for inherent anticipation and inherency in obviousness are different and the present invention is rejected as obvious, the Court opinion in *In re King* directed to inherent anticipation is not applicable in the present case.

With respect to *In re Grasselli*, the Court reversed the board's obviousness rejection based on the inherent disclosure in the cited reference because the record failed to establish that the inherent disclosure is known to one skilled in the art. The Court specifically stated that "[i]f appellant's catalyst is inherent in the Japanese Patent, it has not been established by the record here and obviousness cannot be predicated on that which is unknown. Thus we reverse the board's rejection on the Japanese Patent." (*Id.* 776).

Therefore, the current case law including the cases cited by the examiner clearly sets forth the standard for obviousness rejections based on inherency, *i.e.*, one has to establish that such inherency is known or necessarily known to one skilled in the art.

Applicants respectfully submit that for the present case, the examiner has 1) failed to establish the alleged "inherent teaching" in Ma, and 2) failed to establish such alleged "inherent teaching" was known or necessarily known to one skilled in the art prior to the present invention.

The Office Action states that Ma disclosed IgG based antibodies and these IgG based antibodies, "by their very nature stimulate a humoral immune response regardless of the motivation behind its application." Applicants respectfully point out that the IgG based antibodies disclosed by Ma are all of murine origin and were used to treat dental caries in

humans. One skilled in the art would have realized that these murine IgG based antibodies would not be able to work with the human immune system to elicit a humoral immune response in human. Therefore, even though Ma discloses IgG based antibodies, it does not inherently disclose antibodies that elicit the humoral immune response required by the present invention.

The examiner has not provided any other bases for the rejection based on inherency. Nevertheless, for the purpose of argument even if we assume that Ma in combination with Adair "inherently disclosed" humanization of antibodies provided by Ma, the examiner has yet to establish that one of the specific indications of such "inherently disclosed" humanized antibodies was known or necessarily known to one skilled in the art, *e.g.,* one particular type of the inherently disclosed antibodies can be used to eliciting humoral immune responses for the treatment or prevention of dental caries.

According to Ma, the antibodies provided by Ma are useful for treating dental caries by causing bacterial aggregation, but not by eliciting humoral immune response. Therefore, one skilled art would have viewed the "inherently disclosed" humanized antibodies as antibodies that useful for treating dental caries by causing bacterial aggregation, and would not have known or necessarily known that for treating dental caries one should use antibodies to elicit humoral immune responses as described by the present invention.

The present invention is directed to a unique way of treating dental caries, *e.g.,* by using antibodies to elicit a humoral immune response. Simply providing the "inherently disclosed" humanized antibody does not support the proposition that one of the various indications possibly associated with the antibody would have been known or necessarily known to one skilled artisan at the time prior to the present invention. For example, Ma and Adair "inherently disclosed" at least two different types of humanized antibodies, *i.e.,* IgA and IgG. The IgG type is useful for eliciting humoral immune response while the IgA type is not. Other than relying on hindsight, the examiner has yet to show why one skilled artisan would have chosen one "inherently disclosed" antibody over the other, especially in light of the fact that Ma's own teaching promotes IgA over IgG type for the treatment of dental caries.

In addition, the examiner has failed to provide any supporting evidence to show that one skilled artisan would have known or necessarily known at the time prior to the present invention that the assumed "inherently disclosed" humanized antibody would have been capable of eliciting humoral immune responses to cariogenic organisms as required by the present invention. As discussed above, it has been well known that the environment harboring cariogenic organism usually lacks endogenous antibodies that are associated with humoral immune responses; therefore it is uncertain whether chimeric antibodies introduced exogenously would be able to elicit a humoral immune response that was not naturally occurring.

In summary, the examiner has failed to establish that what may be inherent in the prior art, the advantage or indication of which was known or necessarily known to one skilled in the art at the time prior to the present invention. It has long been held by the Court, "that which may be inherent is not necessarily known; obvious cannot be predicted on which is unknown." *In re Spormann* 363 F.2d 444, 150 U.S.P.Q. 449 (CCPA 1966).

X. APPENDIX

Appendix A contains a copy of pending claims 1-4, 6-10, 12, and 17 that are the subject of the present appeal.

Appendix B contains Figure 1 illustrating general antibody structure.

XI. CONCLUSION

The examiner has failed to establish a prima facie case of obviousness for the reasons given above. The rejection of all claims should be reversed.

Respectfully submitted,

Date: 1/27/03

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Enclosures: Appendices A and B

APPENDIX A

1. A method for the treatment and prevention of dental caries in a mammal comprising oral administration of a chimeric monoclonal antibody that specifically binds to a cariogenic organism and elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal, wherein the portion of the monoclonal antibody that binds to the cariogenic organism is derived from a species other than that of the mammal to be treated.

2. The method for treatment and prevention of dental caries of claim 1 wherein the chimeric monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing the chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

3. The method for treatment and prevention of dental caries of claim 2 wherein step c) further comprises synthesis of a nucleic acid construct comprising:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

4. The method for treatment and prevention of dental caries of claim 3 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 3 above.

6. The method for treatment and prevention of dental caries of claim 1 wherein the mammal to be treated is human, and the other species is mouse.

7. A method for treatment and prevention of dental caries in a mammal comprising administration to a subject in need of such treatment a chimeric monoclonal antibody that specifically binds to a cariogenic organism and elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal, wherein the portion of the monoclonal antibody that binds to the cariogenic organism is derived from a species other than that of the mammal to be treated.

8. The method for treatment and prevention of dental caries of claim 7 wherein the monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing a chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

9. The method for treatment and prevention of dental caries of claim 8 wherein the step c) further comprises preparation of a nucleic acid construct that includes:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

10. The method for treatment and prevention of dental caries of claim 9 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 9 above.

12. The method for treatment and prevention of dental caries of claim 8, wherein the mammalian host is a mouse, and the mammal to be treated is a human.

17. The method for treatment and prevention of dental caries of claim 8, wherein the mammal to be treated is a dog or a cat.

APPENDIX B

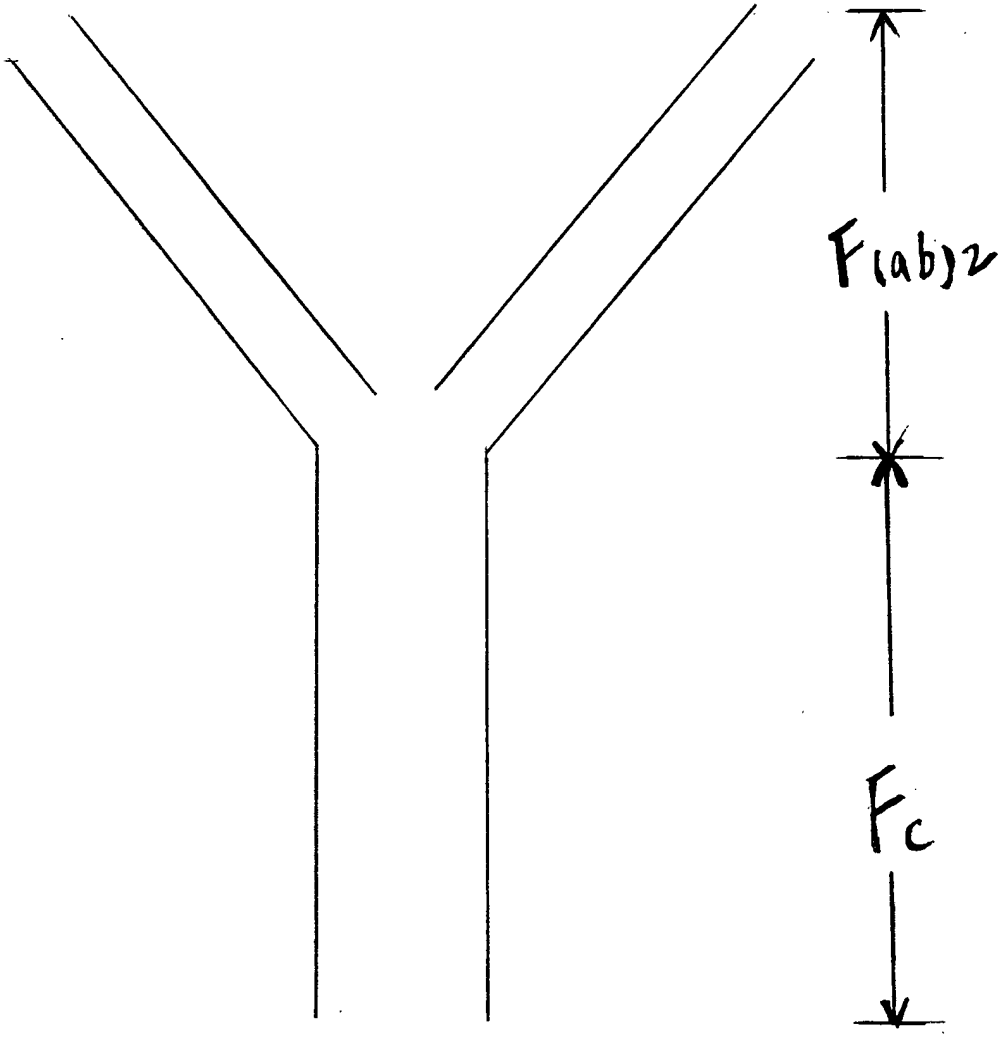

Figure 1